Case Report

Perforated Meckel's Diverticulitis and an Ileal Ulcer in Rheumatoid Arthritis:

The Pathogenic Role of Arterial Thrombosis in these Lesions

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Abstract

Gastrointestinal (GI) tract perforation is a serious complication in patients with rheumatoid arthritis (RA). This complication has been reported in the eras of both disease-modifying anti-rheumatic drugs (DMARDs) and biologics for RA. However, the etiopathogenesis of this condition has not been satisfactorily clarified to date. We experienced the case of an 83-year-old male treated with adalimumab, methotrexate (MTX) and prednisolone (PSL) who developed hematochezia. The operation demonstrated perforated Meckel's diverticulitis and an ileal ulcer; these complications occurred after the interruption of RA treatment for eight weeks. The pathology showed an artery with organized thrombi in the diverticular wall associated with recanalization and a fresh thrombotic arteriole beneath the ileal ulcer, although there was no evidence of arteriosclerosis, angiitis, amyloidosis or infection. The former site of arterial thrombosis was presumed to play an important role in the pathogenesis of perforated Meckel's diverticulitis and the ileal ulcer in this case. The onset of arterial thrombosis during or shortly after the discontinuation of biologic treatment has rarely been described. However, the potential for arterial thrombosis should thus be considered in patients receiving such treatment who present with perforation or ulcers of the GI tract.

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Introduction

GI perforation, including the upper and lower GI tract, has been reported in patients with RA.[1-4] The pathological findings suggest that such cases are associated with treatment with steroids or non-steroidal anti-inflammatory drugs and/or conditions such as amyloidosis or angiitis.[1-4] However, several reports have recently indicated the role of biologics in GI perforation.[2-4] We recently experienced a case of upper GI tract perforation with Meckel's diverticulitis and an ileal ulcer who had been treated with biologics, MTX and low doses of both PSL and one kind of non-steroidal anti-inflammatory drug (NSAID). These events occurred shortly after the interruption of RA treatment. A pathological examination revealed the presence of arterial thrombosis, which was thought to play a crucial role in the pathogenesis of the diverticulitis and ulcer formation. In this report, we present the clinical course and pathological findings of this case and discuss the implications of biologic treatment in the pathogenesis of these lesions.

Case Report

An 80-year-old male (a gynecologist) developed

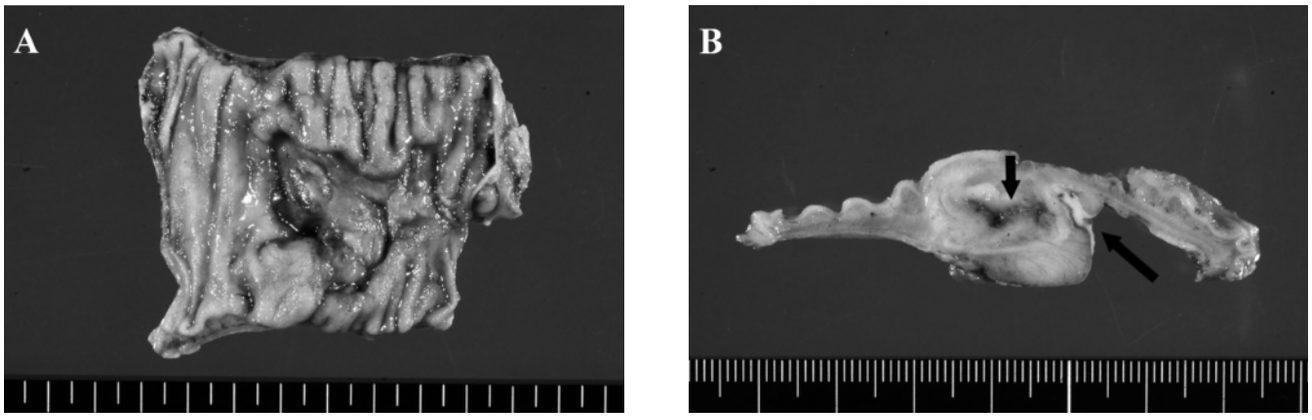

Fig. 1 Macroscopic findings of the perforated Meckel's diverticulitis and ileal ulcer
A: The ileal ulcer is located around the orifice of the diverticulum.
B: The diverticulitis in the distal portion of the diverticulum on a cross-section (short arrow) and the adjacent peritonitis (long arrow).

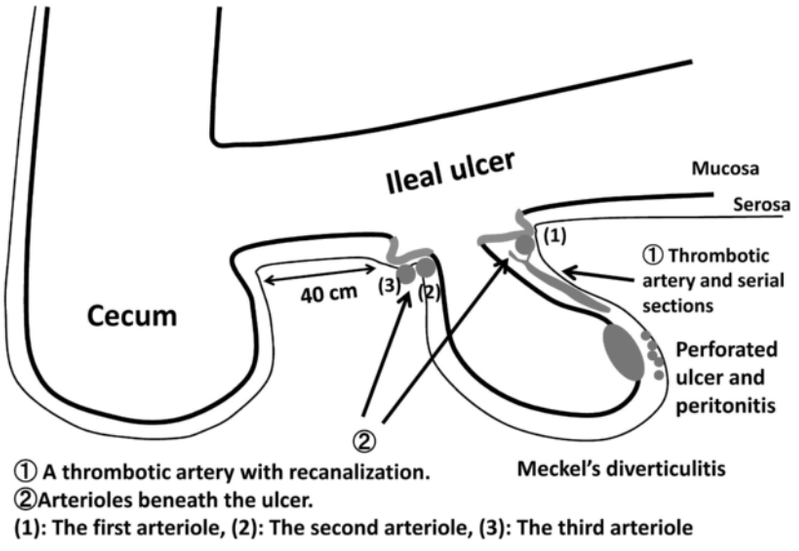

Fig. 2 Illustration of the perforated Meckel's diverticulitis and ileal ulcer
A Meckel's diverticulum located 40cm from the cecum contains an ulcer on the distal portion associated with peritonitis. ①: A small artery located between the site of diverticulitis and the ileal ulcer is studied on serial sections. ②: Three different small arteries and arterioles beneath the ileal ulcer are examined. The pathological findings are described in the Results section.

morning stiffness and polyarthralgia in January 2005, was diagnosed with RA (Stage II, Class 2) in 2008, and was satisfied with the classification criteria for RA of 2010 ACR/EULAR including positivity for anti-cyclic citrullinated protein (CCP) antibodies (Abs).[5] Since the diagnosis of RA, he had been treated with MTX (4 mg/wk) and PSL (5 mg/day) in addition to loxoprofen (120–60mg/day). Although this treatment resulted in good control with only mild arthralgia, the patient wished to be free from arthralgia and subcutaneous injections of adalimumab (40mg/2 weeks) were therefore started in January 2009 to provide better disease control. His condition subsequently improved with no positive findings for thrombosis, including anti-cardiolipin Abs, lupus anticoagulant, thrombocytosis, an elevated D-dimer level, NIDDM, hypertension, etc., at the outpatient clinic. However, he failed to take adalimumab, MTX, PSL and loxoprofen for eight weeks prior to the current admission because he had been unable to visit the hospital after sustaining a minor head contusion from falling down onto the pavement; he remained able to perform activities of daily living at home as usual. He then presented with massive hematochezia, not associated with any apparent abdominal pain or fever, in the middle of February 2012 and was admitted to our university hospital. At that time, he manifested a DAS-CRP level of 7.7 with symptoms of arthritis in the PIP and MCP of the fingers as well as the hands and knees. The main laboratory data are presented in Table 1; no abnormal findings were noted, except for a moderate RA activity. Esophagogastroduodenoscopy and colonoscopy were conducted to identify the site of bleeding; however, these procedures demonstrated no apparent sites of

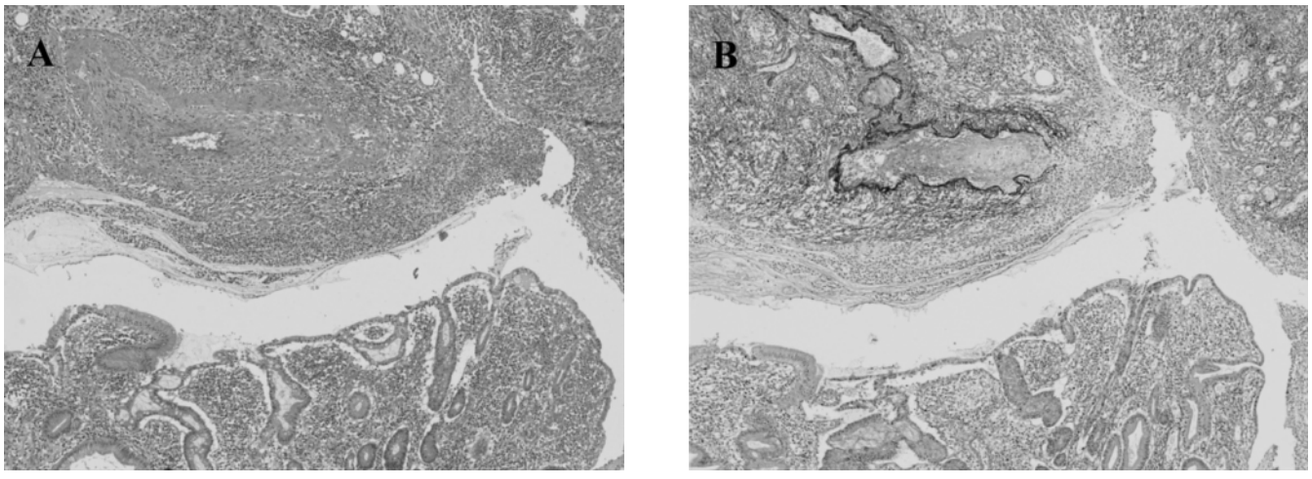

Fig. 3 Meckel's diverticulitis
The distal portion of the diverticulum exhibits an ulcer and ectopic gastric mucosa (A), with an occluded small artery beneath the ulcer (B). (A: HE staining, ×200, B: EVG staining, ×200)

Table 1 Main laboratory data around the time of admission

Hb	10.1 g/dl (11.2～15.2)
WBC	7,400/μl (3,500～9,000)
plts	19.9 × 10^4/μl (14.0～38.0)
urine	Protein (−)
	Sugar (−)
	Occult blood (−)
	Urobilinogen (±)
TP	5.5 g/dl (6.5～8.2)
A1b	2.8 g/dl (3.7～5.2)
AST	19 IU/ml (8–33)
ALT	15 IU/ml (3–30)
ALP	257 IU/ml (104～338)
LDH	205 IU/ml (120～245)
BUN	23.1 mg/dl (8.0～20.0)
Cr	0.7 mg/dl (0.46～0.82)
Total cholesterol	211 mg/dl (150～220)
Triglyceride	106 mg/dl (60～130)
LDL cholesterol	66 mg/dl (0～140)
BNP	19.7 pg/ml (0–18.4)
CRP	6.3 mg/dl (<0.4)
RF	58 IU/ml (<15)
Anti-CCP Ab	20.7 U/ml (<4.5)
MMP-3	236 ng/ml (<36.9–121)
ANA	<40× (<40)
CH50	54 U/ml (30–45)
C1q	1.5 μg/ml (<3.0)
MPO-ANCA	<1.3 U/ml (<9.0)
PR3-ANCA	1.3 U/ml (<3.5)
Anti-CL IgG Ab	1.0 U/ml (0～9.9)
Anti-β2 GPI Ab	<1.3 U/ml (0～9.9)
Pro time	92% (80–100)
PT-INR	1.05
APTT	33.9 sec (27–40)
Fibrinogen	398 mg/dl (200–400)
LAC	1.0 (0～1.3)

bleeding, showing only fresh blood in the cecum. Three weeks later, the patient developed lower abdominal pain and a fever of 39°C. Abdominal surgery was subsequently performed, which revealed the presence of perforated Meckel's diverticulitis and a deep mucosal ulcer at the orifice of the diverticulum in the terminal ileum; nine centimeters of the terminal ileum were thus resected. According to the macroscopic findings, the orifice of the diverticulum was identified to be associated with a well-demarcated ulcer measuring 40mm×35mm in diameter (Fig. 1A), while the distal portion of the diverticulum contained an ulcer with inflammatory changes in the adjacent peritoneum (Fig. 1B). A histological examination of Meckel's diverticulitis and the ileal ulcer was carried out using hematoxylin and eosin (HE), Elastica van Gieson (EVG), and Gram and Grocott's staining. Specifically, the wall of the diverticulum was successively cut at a thickness of 50μm toward the ileal ulcer, thus permitting close observation of the small arteries. Immunohistochemical studies of paraffin-embedded sections using CD31, von Willebrand factor (vWF), tissue factor (TF) and thrombomodulin (TM) were also conducted as previously described.[6] In particular, monoclonal antibodies to CD31, vWF, TM (Dako, Denmark) and TF (Sekisui Diagnostica, CT, USA) were used.

The anatomical relationships between the diverticular thrombotic artery, Meckel's diverticulitis, ileal ulcer and both small arteries and arterioles, as described below, are illustrated in Figure 2. The distal portion of the diverticulum contained an erosive ulcer of the ectopic gastric mucosa and an artery with a fresh thrombus accompanied by disruption of the internal elastic lamina (IEL) (Figs. 3A, B). However, a study of the proximal portion of this artery using serial sections of the diverticulum revealed an artery associated with organized thrombi, although without the destruction of the IEL or apparent arteriosclerosis (Figs. 4A # 1–8, 4B). In addition, further examination

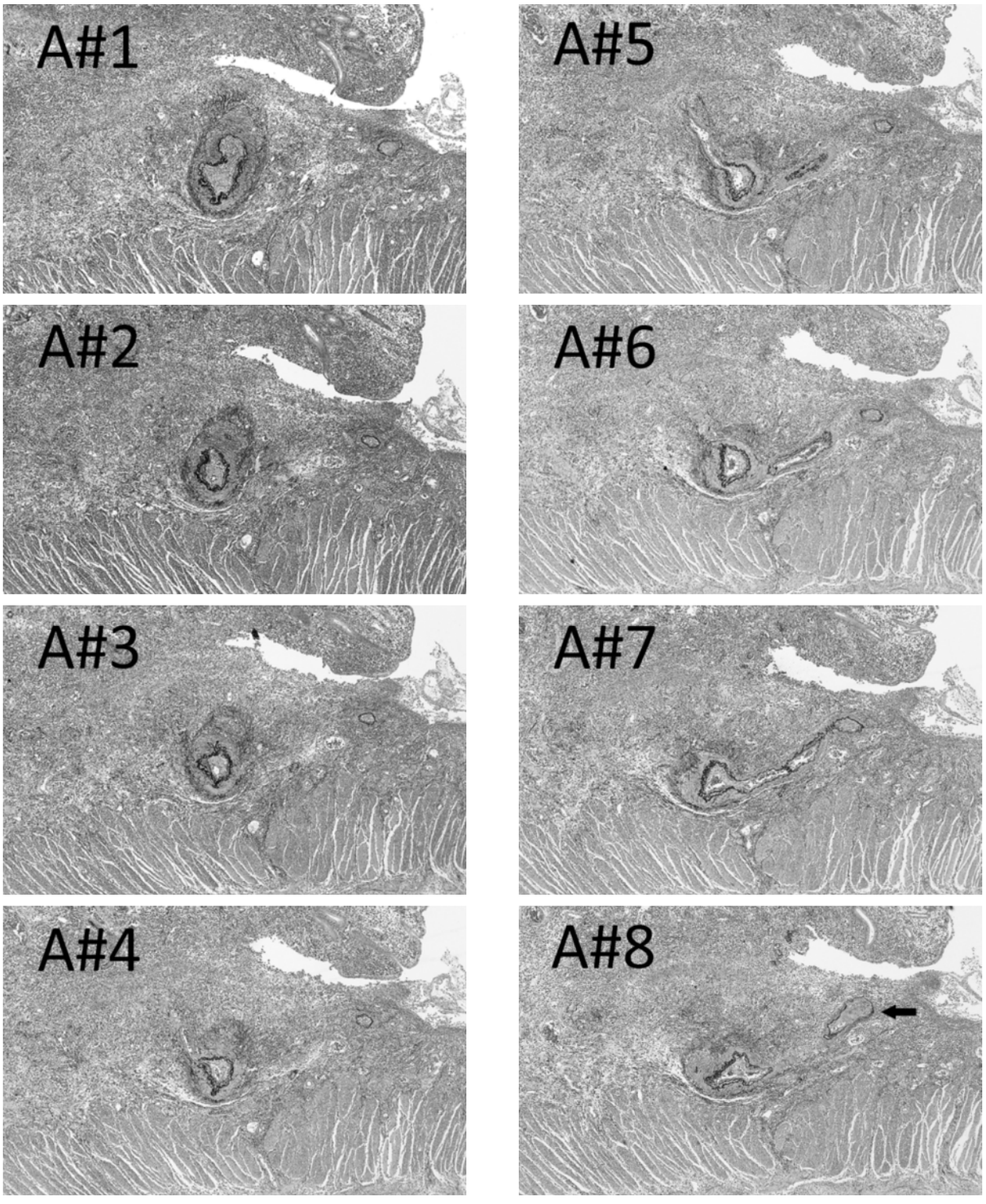

Fig. 4 Serial sections of a thrombotic artery in the diverticulum located toward the ileal ulcer (cut in 50-μm-thickness) (A) and visualization with other types of staining and settings of magnification (B, C)

A: Serial sections of a small artery in the diverticulum wall from proximal # 1 to distal # 8. The artery shows organized thrombi with recanalization in a deeper section (# 2), with bifurcation to a small artery and arteriole in # 5 to # 7 (first branch). The right-directed arteriole is located beneath the ileal ulcer and is occluded by a fresh thrombus (arrow) (# 8) (EVG staining, ×40).

demonstrated only slight infiltration of inflammatory cells in the vessel wall and around the vessel (Fig. 4B). Further serial sections of this artery showed a conserved arterial lumen with bifurcation into the small artery and arteriole (first branch) (Fig. 4A # 5). The arteriole beneath the ileal ulcer contained a relatively fresh thrombus (Fig. 4A # 8). Moreover, the other parts of the sections disclosed two different small arteries and arterioles as second and third branches derived from the diverticular artery. The second small

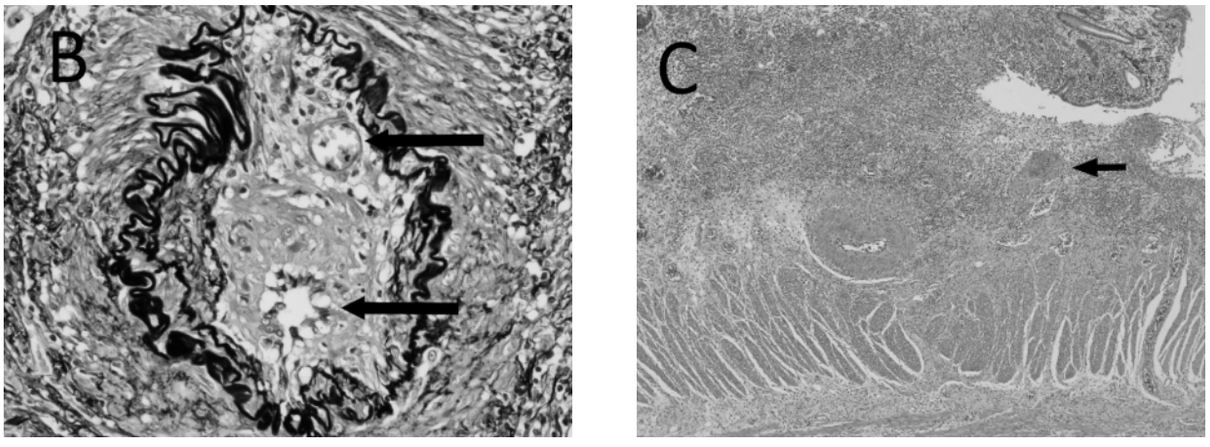

Fig. 4 BC B: Higher magnification view of Figure 4A # 2 showing a recanalized thrombus (arrows) and intact vessel wall with slight infiltration of inflammatory cells around the vessel (EVG staining ×200).
C: HE staining in Figure 4A # 8. A fresh thrombus is observed in the right-directed arteriole (arrow) (HE staining ×40).

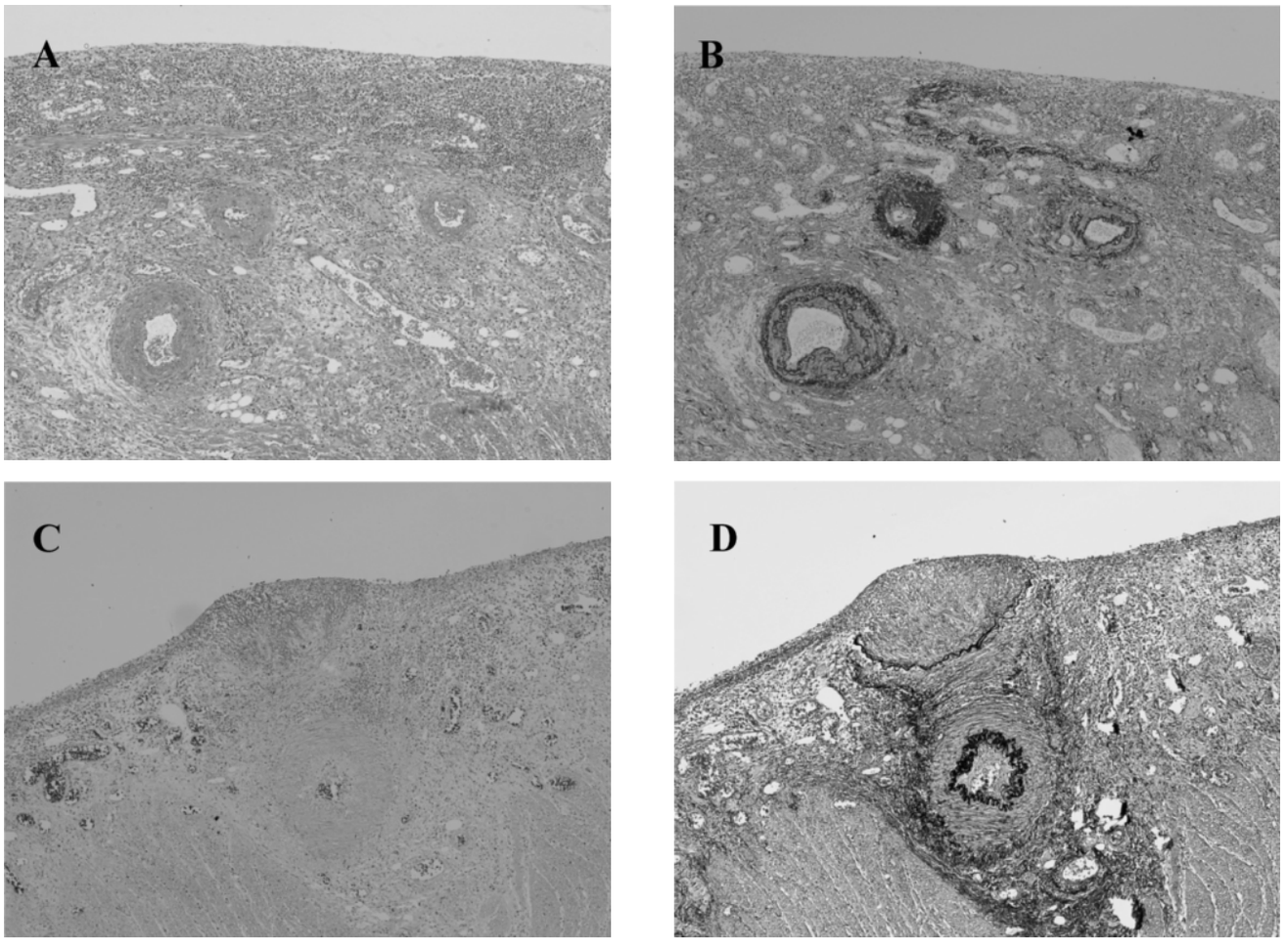

Fig. 5 Ileal ulcer and arterioles/small arteries
A, B : The second branch of the small artery and arteriole shows no thrombosis or arteriosclerosis (A: HE staining, ×100, B: EVG staining, ×100).
C, D : The third branch of the small artery and arteriole demonstrates a partially occluded small artery and eroded arteriole on the surface of the ileal ulcer, including fresh thrombi (C: HE staining, ×100, D: EVG staining, ×100).

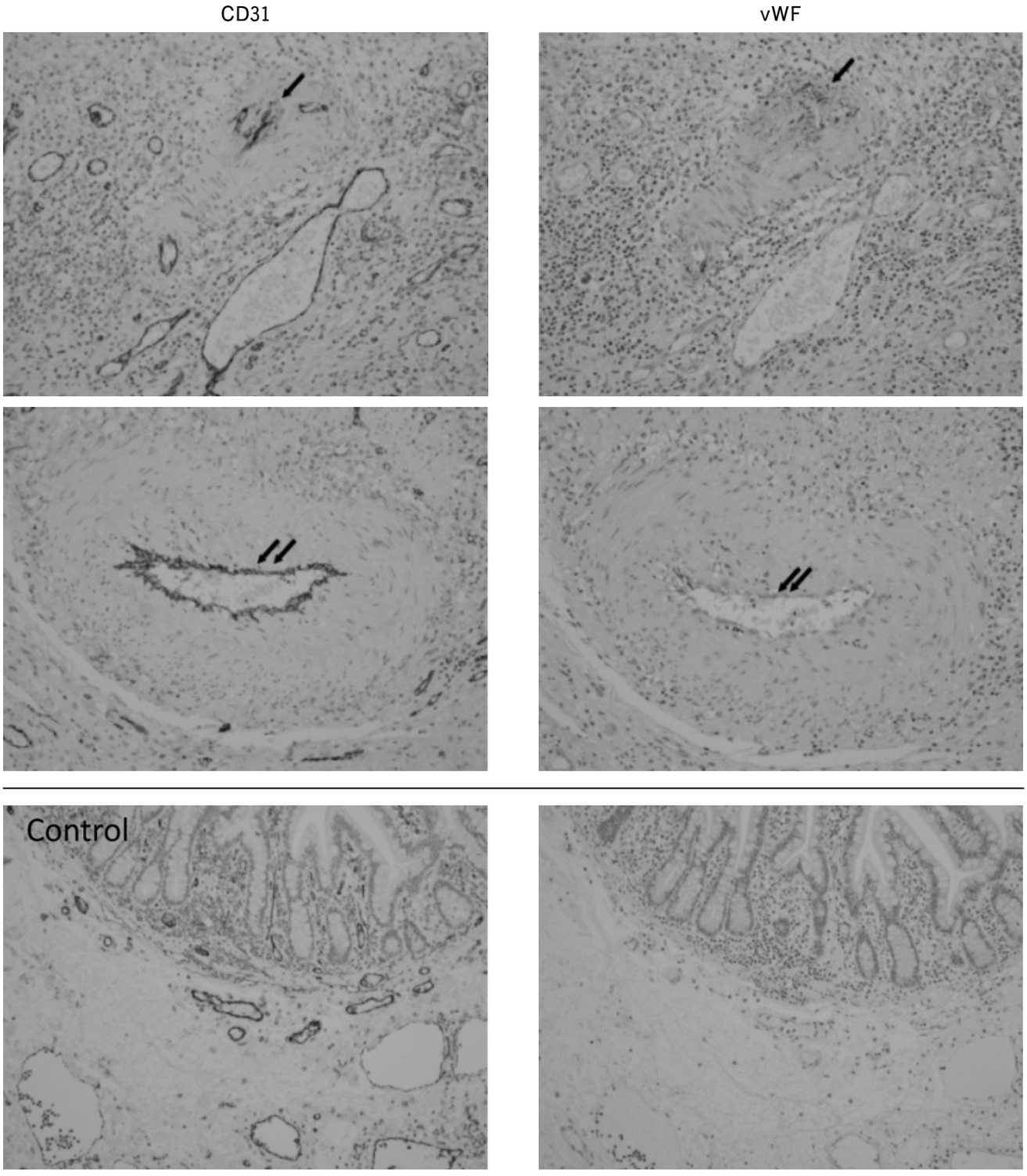

Fig. 6 Expression of CD31 and von Willebrand factor (vWF) in the small arteries and arterioles beneath the ileal ulcer

Patient tissue samples
CD31 staining: Increased staining is observed on the endothelial cell surface of an arteriole with a fresh thrombus (arrow). The small artery without the thrombus shows a clear expression (double arrows) (×200).
vWF staining: Positive staining on the endothelial cell surface of an arteriole exhibiting a fresh thrombus (arrow). The small artery displays slightly positive findings (double arrows) (×200).

Control ileum samples
Staining is positive for CD31and negative for vWF (×200).

artery and arteriole were almost intact without thrombus formation (Figs. 5A, B), while the third small artery and arteriole demonstrated an eroded arteriole with a thrombus in the ulcer and a partially occluded small artery with intact IEF (Figs. 5C, D). All these sections around the arteries and arterioles showed acute inflammatory processes associated with the predominant infiltration of neutrophils, but without the formation of either granulomatous tissues or fibrosis. Immunohistochemical studies of the artery near the relatively fresh thrombotic lesion showed an increased expression of both CD31 antigens and vWF on the endothelial surface (Fig. 6), with no demonstrable TF or TM expression. In contrast, the root of the small artery was found to be positive for CD31, with the scant presence of vWF (Fig. 6) and negative for TF which was associated with the slight presence of TM on the endothelial surface (data not shown). Only TF-positive mononuclear cells were found around the arteriole and small artery. Two control cases showed a positive CD31 expression and negative staining for vWF (Fig. 6), with the equivocal presence of TM and negative findings for TF on the endothelial surface.

Discussion

GI perforation, as described in the previous DMARD era, has also been reported in RA patients treated with biologics.[2–4] The post-marketing surveillance of biologics in Japan disclosed 20 patients with GI perforation as of July 2013, five of whom were identified to have upper GI tract perforation.[7–11] This survey assessed the effects of infliximab, etanercept, adalimumab and tocilizumab in patients treated between 1993 and 2013. Notably, the incidence of GI perforation appears to vary among these drugs, although the exact incidence of GI perforation associated with each biologic requires further investigation. In addition, the pathogenesis of GI perforation during treatment with biologics has not been described in detail and remains unclear. Therefore, it is worthwhile to describe each case thoroughly, including the pathological findings and clinical course. The Meckel's diverticulum in this case involved an erosive ulcer, adjacent peritonitis and the presence of organized thrombi in an artery in the diverticular wall. The arterial thrombosis noted in the diverticulum, as evaluated using serial sections, is presumed to be the cause of the patient's perforated Meckel's diverticulitis. Furthermore, although the ileal ulcer was fairly large in size, it was also thought to be caused by the diverticular artery which was studied with serial sections. In fact, the development of peptic ulcer in the ectopic gastric mucosa of the Meckel's diverticulum or infection with bacteria or fungi is not thought to be causative factors for the perforated diverticulitis associated with ileal ulcer. Indeed, the ulcer in the diverticulum was not deeply or widely ulcerated whereas the ileal ulcer was well demarcated. Moreover, neither angiitis nor amyloidosis was observed on the pathologic examination and these factors did not play a pathogenetic role in the development of the present lesions. Treatment with steroids and/or loxoprofen is also not assumed to be the cause of such lesions when taken at low doses.[2–4,12,13] Therefore, the thrombosis formation observed in the non-arteriosclerotic small artery of the Meckel's diverticular wall is strongly considered to have induced the diverticulitis which thus led to massive bleeding in the initial phase, as is typical in cases of Meckel's diverticulitis. At the time of the operation, three weeks had already passed after the development of arterial thrombosis. This time delay allowed for the progression to organized thrombi, although without destruction of the IEL, as well as ulcer formation around the orifice of the diverticulum due to ischemia of the root artery. This pathogenesis of the ileal ulcer was evidenced by the presence of a relatively fresh thrombus in the arteriole beneath the ulcer and the observation of a partially conserved arteriole lumen, as shown in Figures 4 and 5. These findings are furthermore supported by the results of immunohistochemical staining showing an increased expression of both CD31 antigens and vWF on the endothelial surface of the arteriole. In contrast, it is noteworthy that the patient exhibited no laboratory data indicating hypercoagulability or clinical findings suggesting other sites of thrombosis in additional organs. Dehydration and prolonged bed rest are not thought to be causes of arterial thrombosis in this case, as the patient was able to perform his daily activities at home as usual. In addition, no cardiac disorders or apparent marked atherosclerosis, which may result in arterial embolism, were not identified on routine examinations or computed tomography of the chest or abdomen.

The incidence of venous thrombosis in RA patients is reported to be high compared with that observed in patients with other diseases.[14,15] Surprisingly, a French surveillance study recently shows that arterial thrombosis has a similar incidence to venous thrombosis in RA patients treated with biologics.[16] Furthermore, the development of arterial thrombosis in association with biologic treatment has been described in several previously reported cases.[17–20] The onset of arterial thrombosis during the infusion of biologics is reported to be related to angiospasms, whereas the occurrence of this condition shortly after the discontinuation of biologic therapy is not clear and may simply be coincidental. However, it can be speculated that the rebound production of TNF-α has an effect on vascular-related factors, potentially leading to thrombosis.[21,22] Therefore, studies of further cases will help to clarify the relationship between arterial thrombosis and treatment with biologics.

We herein reported a rare case of arterial thrombosis in a patient with RA involving the pathogenesis of perforated Meckel's diverticulitis and an ileal ulcer and discussed the presumed pathogenetic role of biologics in the development of these lesions.

This case was presented at the 18th Research Conference of Vascular Pathology in Japan held on October 19-20, 2013 in Sapporo, Japan.

Conflicts of Interest: None

Disclosures: Information regarding the side effects of each drug was obtained from the following pharmacological companies: Tanabe-Mitsubishi, Takeda-Pfizer, Eisai-Abbvie and Chugai. We obtained permission from each company to present these data in the literature.

Ethics: This case report was reviewed and approved by the ethics committee of Kyorin University (No.; H25-145). Informed consent for the publication of this case was obtained from the patient and his daughter.

References

1. Cafardi J, Rakatansky H, Alarcón G. Gastrointestinal manifestations of rheumatoid arthritis. In: Asherson R, Font J, Ramos-Casals M, et al.(eds). Handbook of Systemic Autoimmune Diseases. Vol.8. Amsterdam: Elsevier BV, 2008: 109-117.
2. Curtis JR, Xie F, Chen L, et al. The incidence of gastrointestinal perforations among rheumatoid arthritis patients. Arthritis Rheum 2011; 63: 346-351.
3. Gout T, Ostör AJ, Nisar MK. Lower gastrointestinal perforation in rheumatoid arthritis patients treated with conventional DMARDs or tocilizumab: a systematic literature review. Clin Rheumatol 2011; 30: 1471-1474.
4. Curtis JR, Lanas A, John A, et al. Factors associated with gastrointestinal perforation in a cohort of patients with rheumatoid arthritis. Arthritis Care Res (Hoboken); 64: 1819-1828.
5. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62: 2569-2581.
6. Nakabayashi K, Sumiishi A, Sano K, et al. Tubulointerstitial nephritis without glomerular lesions in three patients with myeloperoxidase-ANCA-associated vasculitis. Clin Exp Nephrol 2009; 13: 605-613.
7. INFLIXIMAB (Remicade) [prescribing information]. http://medical.mt-pharma.co.jp/di/remicade/remicade/anzen/anzen01/anzen01.shtml. Accessed 22January 2014 (in Japanese).
8. EMBREL (etanercept) [prescribing information]. Total statistical analysis of etanercept after the post-marketing. Published in July, 2010. by Takeda-Pfizer pharmacologic company (in Japanese).
9. Koike T, Harigai M, Ishiguro N, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3,000 patients. Mod Rheumatol 2012; 22: 498-508.
10. HUMIRA (adalimumab) [prescribing information]. Pharmaceuticals and medical devices agency web site. http://www.info.pmda.go.jp/downfiles/ph/PDF/112130_3999426G1024_2_03.pdf. Accessed 22 January 2014 (in Japanese).
11. Koike T, Harigai M, Inokuma S, et al. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol 2014; 41: 15-23.
12. Morris CR, Harvey IM, Stebbings WS, et al. Incidence of perforated diverticulitis and risk factors for death in a UK population. Br J Surg 2008; 95: 876-881.
13. Mpofu S, Mpofu CM, Hutchinson D, et al. Steroids, non-steroidal anti-inflammatory drugs, and sigmoid diverticular abscess perforation in rheumatic conditions. Ann Rheum Dis 2004; 63: 588-590.
14. Mameli A, Barcellona D, Marongiu F. Rheumatoid arthritis and thrombosis. Clin Exp Rheumatol 2009; 27: 846-855.
15. Matta F, Singala R, Yaekoub AY, et al. Risk of venous thromboembolism with rheumatoid arthritis. Thromb Haemost 2009; 101: 134-138.
16. Petitpain N, Gambier N, Wahl D, et al. Arterial and venous thromboembolic events during anti-TNF therapy: a study of 85 spontaneous reports in the period 2000-2006. Biomed Mater Eng 2009; 19: 355-364.
17. Urayama S, Kawabe Y. A case of refractory rheumatoid arthritis with ileus and acute thrombotic occlusion in leg artery after treatment with anti TNF-α. antibody therapy. Kyusyu Rheumachi 2003; 22: 116-119. (in Japanese, Abstract in English)
18. Casallo Blanco S, Aragón Díez A, Marcos Sánchez F, et al. Infliximab and acute myocardial infarction. An Med Interna 2005; 22: 301-302.
19. Abedin M, Scheurich D, Reimold SC, et al. Acute coronary syndrome after infliximab infusion. Cardiol Rev 2006; 14: 50-52.
20. Mehta SJ, Bergerb J, Tanga KH. Peripheral arterial thrombosis following administration of infliximab for Crohn disease. [Grand Rounds. Gastroenterology 2010; 10: 78-81. Web site]
21. Conway EM, Bach R, Rosenberg RD, et al. Tumor necrosis factor enhances expression of tissue factor mRNA in endothelial cells. Thromb Res 1989; 53: 231-241.
22. Mackman N. Role of tissue factor in hemostasis, thrombosis, and vascular development. Arterioscler Thromb Vasc Biol 2004; 24: 1015-1022.